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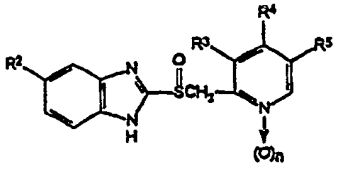
(54) Title: PROCESS FOR THE PREPARATION OF 2-[[(2-PYRIDINYL)METHYL]SULFINYL]-1H-BENZIMIDAZOLES AND NOVEL COMPOUNDS OF USE FOR SUCH PURPOSE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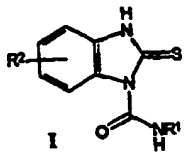
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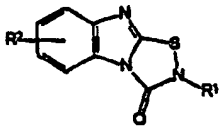
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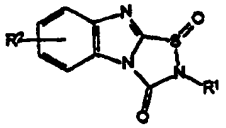
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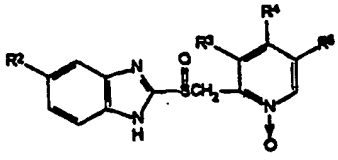
(Va)

(57) Abstract

2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of general formula (V) wherein R^2 represents H, OCH_3, $OCHF_2$ or CF_3, R^3 represents H, CH_3 or OCH_3, R^4 represents H, OCH_3, OCH_2CF_3, halo or nitro, R^5 represents H, CH_3 or OCH_3, and n is 0 or 1, or salts thereof, are prepared by a new process proceeding via novel intermediates of general formulae (I), (II), (III) and (Va) wherein R^1 represents branched or straight C_{1-8}-alkyl, C_{3-8}-cycloalkyl, aryl, aralkyl having 1-8 C-atoms in the alkyl moiety, or a 5- or 6-membered heterocyclic group having one, two or three hetero atoms selected from nitrogen, sulfur and oxygen in the heterocyclic ring. The compounds of formula (V) are biologically active and/or may be used as intermediates in the synthesis of biologically active compounds.

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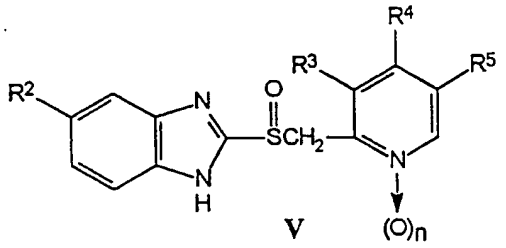
Process for the preparation of 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazoles and novel compounds of use for such purpose.

The present invention relates to a process for the preparation of 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula V



V

wherein

R^2 represents H, OCH_3, $OCHF_2$ or CF_3,

R^3 represents H, CH_3 or OCH_3,

R^4 represents H, OCH_3, OCH_2CF_3, halo or nitro,

R^5 represents H, CH_3 or OCH_3, and

n is 0 or 1,

and salts thereof.

Furthermore, the invention relates to novel compounds of use for such purpose.

The above mentioned compounds of formula V are biologically active and/or may be used as intermediates in the synthesis of biologically active compounds.

The compounds, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole), 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole), 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (timoprazole) and 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (pantoprazole), being known as gastric acid secretion inhibiting agents, are examples of biologically active compounds of the general formula V.

With a few exceptions, the compounds of formula V wherein n is 1, are novel compounds. The present invention provides an elegant new synthesis for the preparation of these compounds, which proceeds in three steps via novel cyclic intermediates and provides the compounds in excellent yields. The three steps may even be carried out in situ as a one-pot process. In an optional step of the process, the compounds of formula V, wherein n is 1, are converted into the corresponding compounds of formula V, wherein n is 0, by reduction.

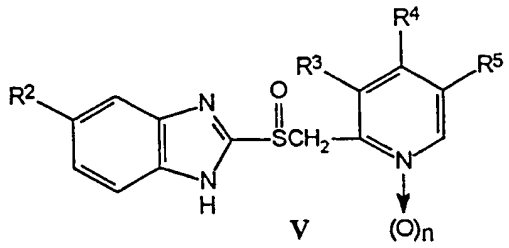
The unsubstituted compound of formula V, wherein n is 1, i.e. the compound 2-[[(1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is described in FR 2 567 123 A1, Example 13, yet without indication of specific process details. FR 2 567 123 A1 includes no description of any other 2-[[(1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazoles or their preparation. No conversion of the compound to the corresponding 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is described either.

The compound of formula V wherein n is 1, R^2 and R^5 are hydrogen, R^3 is methyl and R^4 is 2,2,2-trifluoroethoxy, i.e. the compound 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-1-oxido-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole-N-oxide), is described in ES 2 063 705 B1 as being obtained as an impurity when the compound 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzimidazole is oxidized into 2-[[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (lansoprazole), using m-chloroperbenzoic acid or hydrogen peroxide in the presence of vanadium compounds as oxidation agent. There is no mentioning of the N-oxide being isolated or converted into lansoprazole.

Besides, the compound of formula V wherein n is 1,

R^3 and R^5 represent CH_3, and R^2 and R^4 represent OCH_3, i.e. the compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole-N-oxide), has been reported as having been found as a metabolite of omeprazole in rats, CA 124:306394, Yakubutsu Dotai, 11(1), 45-56 (Japanese) 1996.

The present invention provides a new process for the preparation of 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula V



V

wherein

R^2 represents H, OCH_3, $OCHF_2$ or CF_3,

R^3 represents H, CH_3 or OCH_3,

R^4 represents H, OCH_3, OCH_2CF_3, halo or nitro,

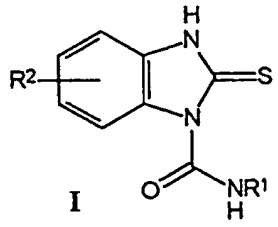
R^5 represents H, CH_3 or OCH_3, and

n is 0 or 1,

and salts thereof,

which process comprises the steps of:

i) cyclizing a 2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide of the general formula I



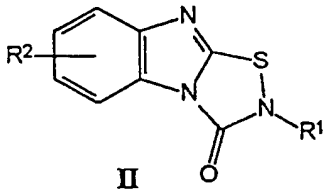
I

wherein R^1 represents branched or straight C_{1-8}-alkyl, C_{3-8}-cycloalkyl, aryl, aralkyl having 1-8 C-atoms

in the alkyl moiety, or a 5- or 6-membered heterocyclic group having one, two or three hetero atoms selected from nitrogen, sulfur and oxygen in the heterocyclic ring, and

R^2 have the same meanings as defined for formula V and is located in the 5- or 6-position of the benzimidazole nucleus,

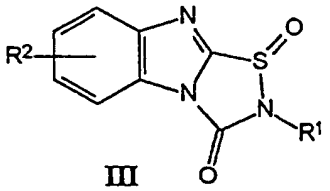
by oxidation in a suitable solvent so as to form a 1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one of the general formula II,



II

wherein R^1 and R^2 are as defined above, and the R^2 group is located in the 6- or 7-position of the condensed ring,

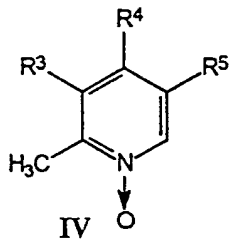
ii) oxidizing the obtained compound of formula II so as to form a 1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide of the general formula III,



III

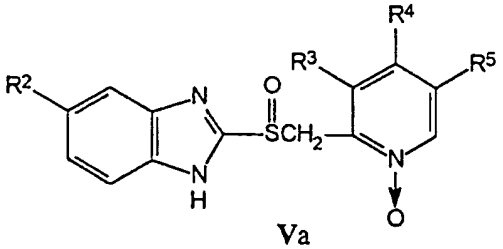
wherein R^1 and R^2 are as defined above, and the R^2 group is located in the 6- or 7-position of the condensed ring, and

iii) reacting the obtained compound of formula III with a pyridine-N-oxide of the general formula IV



IV

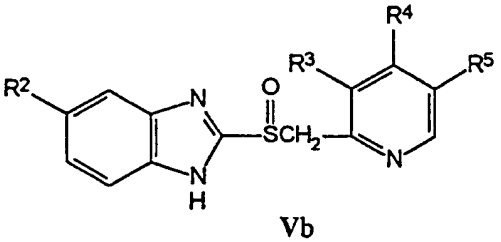
wherein R^3, R^4 and R^5 are as defined above, in the presence of an alcoholate, so as to form a 2-[(2-pyridinylmethyl)sulfinyl]-1H-benzimidazole derivative of the general formula Va



Va

wherein R^2, R^3, R^4 and R^5 are as defined above, and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa, a compound of any of the formulae I, II, III and Va, if desired, being converted into a different compound of said formula before the reaction in the next step is carried out, and furthermore, if desired,

iv) reducing the obtained compound of formula Va or a salt thereof into a compound of the general formula Vb,



Vb

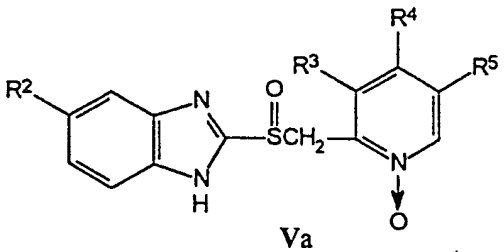
wherein R^2, R^3, R^4 and R^5 are as defined above,

and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa.

The synthesis of addition products of the unsubstituted benzimidazolinethione and isocyanates and the cyclization of the addition products by treatment with bromine/triethylamine, sulfurylchloride or thionylchloride has been described in Tetrahedron, Vol. 39, No. 13, pp. 2311 - 2314, (1983), D. Martin and F. Tittelbach, "Synthesen von Benzimidazolo[1,2-d](1,2,4)-thiadiazolinen". However, the compounds of formula II wherein R^2 is other than hydrogen, appear to be novel compounds and as such represent a particular aspect of the invention. Also the compounds of formula I wherein R^2 is other than hydrogen appear to be novel compounds and as such represent a particular aspect of the invention.

The oxidation of sulphenamides into sulphinamides has been described in e.g. Houben-Weyl," Methoden der Organischen Chemie", Vol. E11, p. 655, (1985) and Patai, "The Chemistry of Sulphinic Acids", p. 259 and pp. 609-10 (1990). However, the compounds of formula III appear not only to be novel, but also to represent a novel cyclic structure. To our knowledge, the entire group of 1,2,4-thiadiazolo[4,5-a]"fused ring"-3(H)-one-1-oxides are compounds not having been described prior to the present invention. Thus, also the compounds of formula III represent a particular aspect of the invention.

By reaction of the novel cyclic compounds III with the pyridine-N-oxide of formula IV in the presence of an alcoholate, a ring opening takes place whereby the compounds of formula V, wherein n is 1, i.e. the compounds of the general formula Va



Va

wherein R^2, R^3, R^4 and R^5 are as defined above, are formed.

To our knowledge, compounds of formula Va have not been used for the preparation of compounds of formula Vb before, and accordingly the use of a compound of formula Va for such purpose represents a particular aspect of the invention.

The starting compounds of formula I, some of which are novel compounds, may be prepared using the synthesis described in the above mentioned Tetrahedron paper, starting from known compounds and/or from novel compounds, which may be obtained using art known processes.

As mentioned above, R^1 represents branched or straight C_{1-8}-alkyl, preferably C_{1-6}-alkyl, such as methyl, ethyl, propyl, incl. n-propyl and i-propyl, butyl, incl. n-butyl, sec.-butyl and tert.-butyl, pentyl, incl. n-pentyl and tert.-pentyl, hexyl, heptyl and octyl, C_{3-8}-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclohexyl, aryl, such as optionally substituted phenyl or naphthyl, aralkyl having 1-8, preferably 1-6 C-atoms in the alkyl moiety, such as optionally substituted benzyl, or an optionally substituted 5- or 6-membered heterocyclic group having one, two or three hetero atoms selected from nitrogen, sulfur and oxygen in the heterocyclic ring. Specific examples of such groups are furyl, thienyl and pyridinyl. The nature of the R^1 group is not particularly critical as long as it allows

the desired reactions to take place. A presently preferred R^1 group is cyclohexyl being easily obtainable through the commercially available cyclohexylisocyanate.

The oxidative cyclisation in step i) is carried out in a suitable solvent, such as a halogenated hydrocarbon solvent, preferably chloroform, methylene chloride, 1,1,1-trichloroethane or a mixture thereof. However, any solvent allowing the desired reaction to take place may be used.

The cyclisation is carried out using an oxidation agent, such as an oxidation agent selected from bromine, chlorine and sulfuryl chloride.

If desired, a base, such as a trialkylamine base and preferably triethylamine, may be added. In a presently preferred embodiment, the cyclisation is carried out using bromine as oxidation agent followed by addition of triethylamine.

In general the oxidative cyclisation will be carried out at a temperature from -20°C - 70°C, and preferably from 0°C - 40°C.

In step ii) the compound of formula II is oxidized into a compound of formula III using a suitable oxidation agent. As an example of suitable oxidation agents, the oxidation agents of peroxy-type, such as oxidation agents selected from peracids, alkylhydroperoxides, benzoylperoxides, hydrogenperoxide, tetraalkylammonium meta-periodates and perborates, can be mentioned. The peracids are preferably optionally substituted perbenzoic acids, such as m-chloroperbenzoic acid.

In general, the oxidation in step ii) is carried out at a temperature from -70°C - 70°C, and preferably from -20°C - 30°C.

As the oxidative cyclisation in step i), the oxidation in step ii) is carried out in a suitable

solvent, such as a halogenated hydrocarbon solvent, preferably chloroform, methylene chloride, 1,1,1-trichloroethane or a mixture thereof. However, any solvent allowing the desired reaction to take place may be used.

The reaction of the compound of formula III with the pyridine-N-oxide of formula IV in step iii) is carried out in the presence of an alcoholate, such as an alkali or alkaline earth metal alcoholate of an aliphatic or alicyclic alcohol. Lithium, sodium and potassium are specific examples of the alkali metals and calcium and magnesium are specific examples of the alkaline earth metals which may be of use in the preparation of the alcoholate. Methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol and t-butanol are specific examples of the aliphatic alcohols, and benzyl alcohol of the alicyclic alcohols which may be of use in the preparation of the alcoholate. A presently preferred alcoholate is an alkali metal alcoholate, particularly potassium t-butoxide.

In general, the reaction in step iii) is carried out at a temperature from -70°C - 50°C and preferably from -30°C - 30°C.

Examples of suitable solvents for the reaction in step iii) are solvents of alkyl- or cycloalkylether type, such as tetrahydrofuran and dioxane, although any solvent allowing the reaction to take place may be used.

In a particular aspect of the invention, all three steps i), ii) and iii) or the steps i) and ii), respectively ii) and iii) may be carried out in situ as a one-pot process.

If desired, a compound of formula Va or a salt thereof as obtained by the above steps i), ii) and

iii), may be reduced into a compound of formula Vb using a suitable reducing agent, a compound of any of the formulae I, II, III and Va, if desired, being converted into a different compound of said formula before the reaction in the next step is carried out.

As examples of reducing agents which may be of use for the reduction of a compound of formula Va into a compound of formula Vb, thiobisamines (diaminosulfanes), dialkoxysulfanes, and catalytical reduction agents such as RaNi/H_2 and Ru-catalysts/H_2 can be mentioned.

In a particularly preferred embodiment, the reduction is carried out using a thiobisamine and particularly thiobismorpholine or thiobispiperidine as reducing agent in the presence of an alcohol and an acid.

Many reducing agents have been suggested for use in the reduction of pyridine-N-oxides into pyridines, cf. e.g. the survey given in Houben-Weyl, "Methoden der Organischen Chemie", Vol. E7b, Part 2, (1992), pp. 543 - 557. However, as far as we know, thiobisamines have not hitherto been suggested for use in the reduction of pyridine-N-oxides into pyridines.

The thiobisamines allow for selective reduction of the N-oxide group in the compounds of formula Va, whereby the compounds of formula Vb may be obtained in almost quantitative yield.

As a further advantage, the reaction takes place under mild conditions. Thus, the reduction can be carried out in an alcoholic solvent, such as in a methanolic and/or ethanolic solvent. Furthermore, the reaction will usually be carried out at a temperature in the range from -10°C - 40°C, although, in principle, there is no hindrance to using temperatures outside this range, such as temperatures in the ranges from

-50°C - -10°C and from 40°C - 70°C.

Usually, the thiobisamine is used in at least an equimolar ratio to the compound of formula Va, although the reaction may proceed at lower ratios such as at ratios of about 0.8. There is no specific upper limit, but for economical reasons molar ratios above 5.0 will normally be avoided. Typically, the molar ratio will not exceed 2.5 and in most cases the molar ratio will be in the range from 1.0 to 1.5.

In a preferred embodiment, the reduction is carried out in the presence of a mineral acid, preferably hydrochloric acid and/or sulphuric acid. The hydrochloric acid may be added as a solution of hydrogen chloride in water, e.g. as concentrated hydrochloric acid or as a solution of hydrogen chloride in a solvent, preferably an alcoholic solvent, such as a solution in methanol and/or ethanol. Also a solution of hydrogen bromide, e.g. in an alcohol as mentioned above, may be used.

In an embodiment being particularly preferred at present, the reduction is carried out in a methanolic and/or ethanolic solvent in the presence of hydrogen chloride under substantially anhydrous conditions.

The invention will now be further illustrated by specific examples which, however, should not be regarded as any limitation of the scope of the invention.

EXAMPLES.

Preparation of starting materials.

Example A. N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide (from 4-methoxy-2-nitroaniline).

N-Cyclohexyl-N'-(4-methoxy-2-nitrophenyl)urea.

4-Methoxy-2-nitroaniline (150 g, 892 mmol), cyclohexylisocyanate (112 g, 892 mmol) og pyridine (45 mL) were dissolved in DMF (dimethylformamide) (1.5 L) and heated to 80°C for 8 h. The formed suspension was cooled to room temperature and ethanol (0.5 L) was added. After cooling on an ice bath, the precipitate was filtered off and washed with ethanol. Drying at 50°C afforded 227 g (87 %) of the title compound as a yellow product. Mp. 233-35°C.

N-Cyclohexyl-N'-(2-amino-4-methoxyphenyl)urea.

N-Cyclohexyl-N'-(4-methoxy-2-nitrophenyl)urea (50.0 g, 170 mmol) was suspended in ethanol (1.5 L) and 10% Palladium on Carbon (5.0 g) was added. The mixture was reduced with hydrogen at 1 atm. and room temperature overnight. Then the reaction mixture was heated to 70°C and the catalyst filtered off. The filtrate was evaporated to 400 mL and cooled to -20°C. The precipitate was filtered off, washed with ethanol and dried at 50°C to give 39.8 g (89 %) of the title compound as a white crystalline product. Mp. 187-88°C.

N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide.

N-Cyclohexyl-N'-(2-amino-4-methoxyphenyl)urea (104.4 g, 397 mmol) and carbondisulfide (66.4 g, 874 mmol) were heated in dry DMF (400 mL) for 41 h at 50°C. The resulting solution was cooled to room temperature and added to water (1250 mL) over 1½ h. After further stirring for 2 h the precipitate was filtered off, washed with water and dried at 60°C to give 118.6 g (98 %) of the title compound as a white crystalline product. Mp. 188-90°C. Recrystallisation from acetone raised the melting point to 198-201°C.

Example B. N-Cyclohexyl-2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide.

The title compound was synthesized from 2-mercaptobenzimidazole and cyclohexylisocyanate essentially following the procedure described by E. Dyer et al., J. Heterocyclic Chem. 6 (1969) 23-28.

Examples illustrating the process according to the invention.

Example 1. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]1H-benzimidazole (Omeprazole-N-oxide).

A. 2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one.

N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide (91.6 g, 300 mmol) (Ex. A) was suspended in chloroform (1.1 L) at room temperature. Bromine (47.9 g, 300 mmol) in chloroform (150 mL) was added over 70 min. at room temperature. Triethylamine (60.6 g, 600 mmol) was added. The formed solution was allowed to cool to room temperature over 1 h and then washed with water (2x1 L). The organic phase was dried over anhydrous sodium sulfate and evaporated in vacuum into a fat crystalline suspension. Ethanol (1.0 L) was added. After cooling to 0°C the precipitate was filtered off, washed with ethanol and dried in vacuum at 35°C to give 87.0 g (96 %) of the title compound as an off-white product. Mp. 181-4°C. Calc. for $C_{15}H_{17}N_3O_2S$: C:59.4%; H:5.7%; N:13.9%; S:10.6%. Found: C:59.2%; H:5.8%; N:13.6%; S:10.6%.

B. 2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide.

2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one (24.3 g, 80 mmol) (Ex. 1A) was suspended in chloroform (160 mL) and cooled on an ice bath. 99% m-CPBA (m-chloroperbenzoic acid) (13.8 g, 80 mmol) was added in small portions over 45 min. at 2-5°C. Then the ice bath was replaced with a 2-propanol - ice bath. After further stirring for 20 min. cold t-butylmethylether (480 mL) was added over 15 min. After cooling to -9°C the precipitate was filtered off and washed with t-butylmethylether. Drying in vacuum at room temperature gave 20.6 g (81 %) of the title compound as a white product. Mp. 155-60°C.

Calc. for $C_{15}H_{17}N_3O_3S$: C:56.4%; H:5.4%; N:13.2%; S:10.0%. Found: C:55.9%; H:5.4%; N:12.8%; S:9.8%.

C. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole-N-oxide).

2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (19.2 g, 60 mmol) (Ex. 1B) was suspended in dry tetrahydrofuran (200 mL) and cooled on an ice bath. Potassium-t-butylate (20.2 g, 180 mmol) was added in portions over 30 min. After further stirring for 5 min., 4-methoxy-2,3,5-trimethyl-pyridine-N-oxide (8.0 g, 48 mmol) was added. The dark green reaction mixture was stirred for 20 min., whereupon acetic acid (7.2 g, 120 mmol) was added. The suspension was evaporated in vacuum to about 100 mL, and the formed residue was dissolved in 1-butanol-toluene (1:4) (100 mL) - water (250 mL). After adjusting the pH to 12 with 1N sodium hydroxide the phases were separated. The water phase was slowly neutralized to pH 7.5 with acetic acid, whereby the title compound

precipitated. After cooling to 0°C the precipitate was filtered off, washed with water and dried to give 12.8 g of crude omeprazole-N-oxide. The crude product was stirred with methanol (150 mL) for 20 min. at room temperature and then cooled to -20°C. The precipitate was filtered off and dried at 60°C to give 11.1 g (64 %) of omeprazole-N-oxide as a white product. Mp. 177-8°C (dec).

Calc. for $C_{17}H_{19}N_3O_4S$: C:56.5%; H:5.3%; N:11.6%; S:8.9%.
Found: C:56.2%; H:5.4%; N:11.7%; S:9.2%.

Example 2. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole N-oxide) (3 steps in situ).

N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide (9.16 g, 30 mmol) (Ex. A) was suspended in chloroform (100 mL) at room temperature. Bromine (4.80 g, 30 mmol) in chloroform (50 mL) was added over a period of 1 h at room temperature. Triethylamine (6.06 g, 60 mmol) was added. The formed solution was cooled to room temperature and washed with water (2x150 mL). The organic phase was dried over anhydrous sodium sulfate and filtered.

The above solution was cooled on an ice bath. 98 % m-CPBA (5.02 g, 29 mmol) was added in portions over 25 min. After further stirring for 40 min. chloroform was distilled off in vacuum. Remaining chloroform was removed by evaporation in vacuum with toluene to give a fat crystalline suspension.

The above suspension was dissolved in dry tetrahydrofuran (150 mL) and cooled on an ice bath. Potassium-t-butylate (13.4 g, 120 mmol) was added in portions over 30 min. After further stirring for 10 min., 4-methoxy-2,3,5-trimethyl-pyridine-N-oxide (5.52 g, 30

mmol) was added. The dark green reaction mixture was stirred for 15 min., whereupon acetic acid was added (5.4 g, 90 mmol). The suspension was evaporated in vacuum, and the formed residue was dissolved in chloroform (100 mL) - water (100 mL). The water phase was extracted with further chloroform (100 mL). The chloroform phases were washed successively with aqueous 10% sodium chloride (50 mL). The combined chloroform phases were dried over anhydrous sodium sulfate and evaporated in vacuum. The residue was taken up in methanol (100 mL) and cooled to -20°C. The precipitate was filtered off, washed with methanol and dried at 50°C to give 4.68 g (43 % over 3 steps) of omeprazole-N-oxide as a white product. Mp. 172-3°C (dec.).

Example 3. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole-N-oxide) (from mixed isomers).

In a similar manner to the procedures described in examples 1 and 2, the title compound was obtained from a mixture of the N-cyclohexyl-2,3-dihydro-5- and -6-methoxy-2-thioxo-1H-benzimidazole-1-carboxamides, prepared from 2-mercapto-5-methoxy-benzimidazole and cyclohexylisocyanate, essentially following the procedure described by E. Dyer et al., J. Heterocyclic Chemistry 6 (1969).23-28.

Example 4. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole).

Pulverized omeprazole-N-oxide (3.61 g, 10.0 mmol) (Ex. 1, 2 and 3) and 4,4'-thiobismorpholine (2.65 g, 13.0 mmol) (synthesized from sodium thiosulfate penta-

hydrate, bromine and morpholine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (70 mL) and cooled on an ice bath. 2.83 N hydrogen chloride in ethanol (7.4 mL, 21.0 mmol) was added. After stirring for 20 min., a clear yellowish solution was obtained. 1N sodium hydroxide (20 mL) was added and the resulting solution was evaporated in vacuum to about 25 mL. To the residue was added water (100 mL) and t-butylmethylether (50 mL). The pH was adjusted to 12 with 1N sodium hydroxide. After stirring for 20 min. at pH 12, the phases were separated and acetic acid was added slowly to the water phase until a pH 7.8 was obtained. After stirring at room temperature the precipitate was filtered off, washed with water and dried at 50°C to give 3.24 g (94 %) of omeprazole as a beige coloured powder. Mp. 153-4°C (dec.). The FTIR-spectra of the product and an authentic sample were identical.

Calc. for $C_{17}H_{19}N_3O_3S$: C:59.1%; H:5.6%; N:12.2%; S:9.3%.
Found: C:59.1%; H:5.6%; N:12.1%; S:9.6%.

Preparation of Omeprazole sodium salt.

Omeprazole (3.45 g, 10.0 mmol) was suspended in methanol (15 mL). Sodium methoxide (540 mg, 10.0 mmol) was added, whereby a new precipitate was formed. After addition of t-butylmethylether (50 mL) the precipitate was filtered off, washed with t-butylmethylether and dried to give 3.7 g of omeprazole sodium salt as a white product.

Example 5. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole).

Example 4 was repeated, but using 1,1'-thiobis-

piperidine (synthesized from sodium thiosulfate pentahydrate, bromine and piperidine as described by J. L. Kice et al, J. Org. Chem. **56** (1991) 5235-6) as the reducing agent. Yield 91%. Mp. 154-5°C (dec.).

Calc. for $C_{17}H_{19}N_3O_3S$: C:59.1%; H:5.6%; N:12.2%; S:9.3%. Found: C:59.1%; H:5.6%; N:12.2%; S:9.5%.

Example 6. 2-[(2-pyridinylmethyl)sulfinyl]-1H-benzimidazole-N-oxide (Timoprazole-N-oxide).

A. 2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one.

N-Cyclohexyl-2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide (27.5 g, 100 mmol) (Ex. B) was suspended in chloroform (400 mL) at room temperature. Bromine (16.0 g, 100 mmol) in chloroform (100 mL) was added over 50 min. at room temperature, whereupon triethylamine (20.2 g, 200 mmol) was added. The formed solution was cooled to room temperature and washed with water (2x300 mL). The organic phase was dried over anhydrous sodium sulfate and then evaporated in vacuum (bath 25°C) into a fat crystalline suspension. Petroleum benzine (bp. 80-100°C) was added. The formed precipitate was filtered off, washed with petroleum benzine and dried in vacuum at 35°C to give 24.3 g (89 %) of the title compound as an off-white product. Mp. 202-6°C.

B. 2-[(2-pyridinylmethyl)sulfinyl]-1H-benzimidazole-N-oxide (Timoprazole-N-oxide) (2 steps in situ).

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one (8.2 g, 30 mmol) (Ex. 6A) was dissolved in chloroform (180 mL) and cooled on an ice bath. 99% m-CPBA (5.19 g, 30 mmol) was added in portions over 25 min. Chloroform was distilled off in vacuum (bath

40°C), until a fat suspension was obtained. Remaining chloroform was removed by evaporation with toluene (100 mL) in vacuum.

The resulting fat suspension of crude "sulfinamide" was dissolved in dry tetrahydrofuran (150 mL) and cooled on an ice bath. Potassium-t-butylate (13.4 g, 120 mmol) was added in portions over 15 min. After further stirring for 10 min., 2-picoline-N-oxide (4.4 g, 40 mmol) was added. The resulting reaction mixture was stirred for 30 min., whereupon acetic acid (5.4 g, 90 mmol) was added. The mixture was evaporated into a fat suspension in vacuum and then methanol (180mL) was added followed by cooling on an ice bath. The precipitate was filtered off, washed with methanol and dried at 50°C to give 5.05 g (62 % over 2 steps) of timoprazole-N-oxide as an off-white product.

Mp. 187-8°C (dec.).

Calc. for $C_{13}H_{11}N_3O_2S$: C:57.1%; H:4.1%; N:15.4%; S:11.7%.

Found: C:57.1%; H:4.1%; N:15.0%; S:11.6%.

Example 7. 2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide.

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one (21.8 g, 80 mmol) (Ex. 6A) was dissolved in chloroform (300 mL) and cooled on an ice bath. 85% m-CPBA (16.2 g, 80 mmol) dissolved in chloroform (100 mL) was added over 35 min. The ice bath was removed and the temperature was allowed to rise to room temperature over 1 h. Chloroform was distilled off in vacuum and low temperature until a fat suspension was obtained. Ethanol (250 mL) was added. After stirring on an ice bath the precipitate was filtered off and washed with cold ethanol. Drying at 30°C gave 20.1 g (87 %) of the title compound as a white product. Mp. 158-160°C.

Calc. for $C_{14}H_{15}N_3O_2S$: C:58.1%; H:5.2%; N:14.5%; S:11.1%.
Found: C:58.2%; H:5.3%; N:14.4%; S:11.2%.

Example 8. 2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (2 steps in situ).

N-Cyclohexyl-2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide (68.8 g, 250 mmol)(Ex. B) was suspended in chloroform (1.0 L) at room temperature. Bromine (40.0 g, 250 mmol) was added over 30 min. at 23-30°C. Triethylamine (50.5 g, 500 mmol) was added. The formed solution was cooled to room temperature and stirred for 1 h and then washed with water (2x500 mL). The organic phase was dried over anhydrous sodium sulfate.

The above solution was cooled on an ice bath. 98 % m-CPBA (43.3 g, 250 mmol) dissolved in chloroform (200 mL) was added over 30 min. at 3-8°C. After further stirring for 30 min. chloroform was distilled off in vacuum (bath 40°C) until a fat suspension (about 250 mL) was obtained. t-Butylmethylether (1 L) was added. After cooling on an ice bath the precipitate was filtered off and washed with t-butylmethylether. Drying at 30°C in vacuum gave 61.2 g (85 % over 2 steps) of the title compound as an off-white product. Mp. 155-7°C.
Calc. for $C_{14}H_{15}N_3O_2S$: C:58.1%; H:5.2%; N:14.5%; S:11.1%.
Found: C:58.6%; H:5.4%; N:14.4%; S:11.2%.

Example 9. 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-1-oxido-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (Lansoprazole-N-oxide).

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (28.9 g, 100 mmol) (Ex. 7 and 8)

was dissolved in dry tetrahydrofuran (300 mL) and cooled on an ice bath. Potassium-t-butylate (28.0 g, 250 mmol) was added in portions over 40 min. After further stirring for 10 min. 2,3-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine-N-oxide (13.3 g, 60 mmol) was added. The reaction mixture was stirred for 15 min, whereupon acetic acid (9.0 g, 150 mmol) was added. The mixture was evaporated in vacuum, and the formed residue was dissolved in 1-butanol-toluene (2:3) (250 mL) - water (250 mL) and acetic acid was added until a pH of 7.0 was obtained. The phases were separated and the organic phase was evaporated. The formed fat suspension was taken up in methanol (200 mL) and cooled on an ice bath. The precipitate was filtered off and washed with methanol followed by water. Drying at 50°C gave 7.9 g of crude lansoprazole-N-oxide. The product was shortly heated to reflux in chloroform (100 mL) and then cooled to room temperature. The crystals were filtered off, washed with chloroform and dried to give 5.3 g (23 %) of lansoprazole-N-oxide as an off-white crystalline product. Mp. 183-3½°C (dec.).
Calc. for $C_{16}H_{14}F_3N_3O_3S$: C:49.9%; H:3.7%; N:10.9%; S:8.3%
Found: C:50.3%; H:3.8%; N:10.8%; S:8.5%.

Example 10. 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (Lansoprazole).

Lansoprazole-N-oxide (3.85 g, 10.0 mmol) (Ex. 9) and 4,4'-thiobismorpholine (2.85 g, 14.0 mmol) (synthesized from sodium thiosulfate pentahydrate, bromine and morpholine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (80 mL) at room temperature. 2.85 N hydrogen chloride in ethanol (8.4 mL, 24 mmol) was added over 3 min. After

stirring for 90 min. the formed solution was evaporated in vacuum to about 25 mL and water (100 mL) was added slowly. The pH was adjusted to 7.5 with 1N sodium hydroxide. After stirring at room temperature the formed precipitate was filtered off and washed with water. Drying at 40°C gave 3.57 g (97 %) of a 94 % pure lansoprazole. Mp. 169-70°C (dec.). Recrystallization from acetone gave analytically pure lansoprazole as a white crystalline product. Mp. 176-7°C (dec.). The FTIR-spectra of the product and an authentic sample were identical.

Calc. for $C_{16}H_{14}F_3N_3O_2S$: C:52.0%; H:3.8%; N:11.4%; S:8.7%
Found: C:52.2%; H:4.0%; N:11.1%; S:8.8%.

Example 11. 2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (11.6 g, 40 mmol) (Ex. 7 and 8) was suspended in dry tetrahydrofuran (150 mL) and cooled on an ice bath. Potassium-t-butylate (13.4 g, 120 mmol) was added in portions over 25 min. After further stirring for 5 min. 4-methoxy-2,3,5-trimethyl-pyridine-N-oxide (5.4 g, 24 mmol) was added. The dark green solution was stirred for 30 min., whereupon acetic acid (4.8 g, 80 mmol) was added. The reaction mixture was evaporated in vacuum to a fat suspension (about 50 mL) and then 1-butanol-toluene (1:3) (80 mL) and water (150 mL) were added. The pH was adjusted to 12 with 11N sodium hydroxide. The water phase was washed with further 1-butanol-toluene (1:3) (80 mL) and then adjusted to pH 7.7 by slowly addition of acetic acid. The resulting suspension was cooled on an ice bath. The precipitate was filtered off and washed with water. Drying at 50°C gave 7.0 g of the crude title

compound. The product was shortly stirred with methanol (80 mL) at room temperature and then cooled to -20°C. The product was filtered off, washed with methanol and dried at 50°C to give 6.3 g (59 %) of the title compound as an off-white powder. Mp. 183-4° (dec.).
Calc. for $C_{16}H_{17}N_3O_3S$: C:58.0%; H:5.2%; N:12.7%; S:9,7%.
Found: C:57.9%; H:5.4%; N:12.8%; S:9.8%.

Example 12. 2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

2-[[(4-Methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (3.31 g, 10.0 mmol) (Ex. 11) and 4,4'-thiobismorpholine (2.86 g, 14.0 mmol) (synthesized from sodium thiosulfate pentahydrate, bromine and morpholine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (75 mL) and cooled on an ice bath. 2.83 N hydrogen chloride in ethanol (7.4 mL, 21.0 mmol) was added. The reaction was monitored by HPLC. After stirring for 1½ h and 2½ h further thiobismorpholine (0.82 g and 0.41 g) and 2.83 N hydrogen chloride in ethanol (2.8 mL and 1.4 mL) was added. After further stirring for 30 min. 1N sodium hydroxide (33 mL) was added. The reaction mixture was evaporated in vacuum to about 35 mL and then water (100 mL) and t-butylmethyl-ether (50 mL) were added. The pH was adjusted to 12 with 1N sodium hydroxide. After stirring at pH 12.0 for 5 min. the phases were separated. The water phase was washed with t-butylmethylether (50 mL) and then acetic acid was added slowly until pH 8.0. The formed suspension was extracted with 1-butanol-toluene (1:1) (120 mL) at 30°C. The organic phase was dried over anhydrous sodium sulfate and then evaporated in vacuum to about 35 mL. Cooling to 5°C, filtration, washing with 1-

butanol and drying at 50°C gave 2.41 g (77 %) of the title compound as a white crystalline product. Mp. 164-5°C (dec.).

Calc. for $C_{16}H_{17}N_3O_2S$: C:60.9%; H:5.4%; N:13.3%; S:10.2%. Found: C:61.1%; H:5.6%; N:13.3%; S:10.0%.

Another crop 0.21 g (7 %) of the title compound (96 % purity) could be obtained from the mother liquor.

Example 13. 5-Methoxy-2-[[(4-chloro-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

The title compound was prepared in 3 steps from N-cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide and 4-chloro-2,3,5-trimethyl-pyridine-N-oxide in 40 % yield essentially following the procedure described for omeprazole-N-oxide (Ex. 2). Mp. 188-9°C (dec.).

60MHz ^{1}H-NMR (d_6-DMSO): δ 2.2 (s, 3H, CH_3), δ 2.3 (s, 3H, CH_3), δ 3.8 (s, 3H, CH_3), δ 4.8 (broad s, 2H, CH_2), δ 6.7-7.0 (m, 2H), δ 7.3-7.5 (m, 1H), δ 8.3 (1H).

Example 14. 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole N-oxide).

A mixture of 5-methoxy-2-[[(4-chloro-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (2.196 g, 6 mmol) (Ex. 13), potassium tert.-butylate (3.36 g, 30 mmol), tert.-butyl ammonium bromide (5.76 g, 18 mmol), methanol (36 mL) and dimethyl sulfoxide (12 mL) was heated to reflux for 18 h. HPLC chromatogram (area %) indicates 67 % yield of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and 6 % unconverted 5-methoxy-2-[[(4-chloro-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]-

sulfinyl]-1H-benzimidazole.

The reaction mixture was poured into water (40 mL), and pH was adjusted to 7.0 with acetic acid (1.35 mL). Then chloroform (50 mL) was added. After separation of the water phase, the chloroform phase was washed with water (2 x 50 mL) and dried over magnesium sulfate. After removal of the magnesium sulfate by filtering, hexane in excess (50 mL) was added. The reaction mixture was left for crystallisation for 1 h, after which the crystals were removed by filtering, washed with hexane (25 mL) and dried.

Yield of crude product: 844 mg of white crystals. Mp. 169 - 70 °C. Purity according to HPLC (area %), 90 %.

Calc. for $C_{17}H_{19}N_3O_4S$: C:56.5%; H:5.3%; N:11.6%
Found: C:55.5%; H:5.1%; N:11.3%

The NMR data correspond to those of an authentic sample.

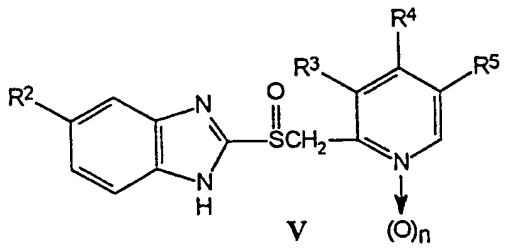
From the mother liquor a further crop of 131 mg of white crystals was isolated. Mp. 168 - 70 °C. Purity according to HPLC: 88.5 %.

Total yield 975 mg.

In the preceding the invention has been described by means of specific examples of preferred embodiments. However, it will be appreciated by a person skilled in the art that various modifications can be made without deviating from the spirit and scope of the invention.

PATENT CLAIMS

1. A process for the preparation of 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula V



V

wherein

R^2 represents H, OCH_3, $OCHF_2$ or CF_3,

R^3 represents H, CH_3 or OCH_3,

R^4 represents H, OCH_3, OCH_2CF_3, halo or nitro,

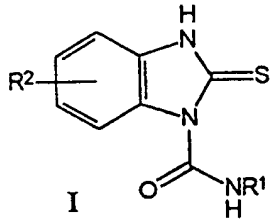
R^5 represents H, CH_3 or OCH_3, and

n is 0 or 1,

or salts thereof,

c h a r a c t e r i z e d in comprising the steps of:

i) cyclizing a 2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide of the general formula I

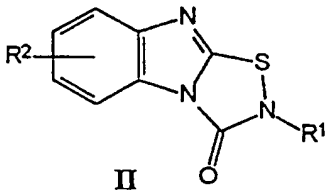


I

wherein R^1 represents branched or straight C_{1-8}-alkyl, C_{3-8}-cycloalkyl, aryl, aralkyl having 1-8 C-atoms in the alkyl moiety, or a 5- or 6-membered heterocyclic group having one, two or three hetero atoms selected from nitrogen, sulfur and oxygen in the heterocyclic ring, and

R^2 have the same meanings as defined for formula V and is located in the 5- or 6-position of the benzimidazole nucleus,

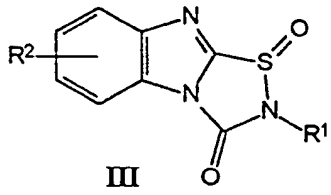
by oxidation in a suitable solvent so as to form a 1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one of the general formula II,



II

wherein R^1 and R^2 are as defined above, and the R^2 group is located in the 6- or 7-position of the condensed ring,

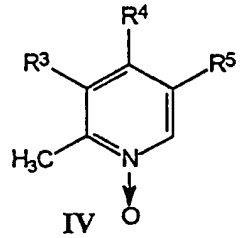
ii) oxidizing the obtained compound of formula II so as to form a 1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide of the general formula III,



III

wherein R^1 and R^2 are as defined above, and the R^2 group is located in the 6- or 7-position of the condensed ring, and

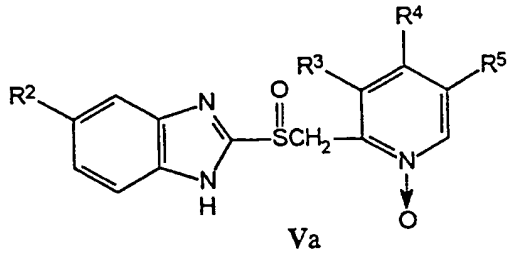
iii) reacting the obtained compound of formula III with a pyridine-N-oxide of the general formula IV



IV

wherein R^3, R^4 and R^5 are as defined above, in the presence of an alcoholate, so as to form a 2-[(2-pyridinylmethyl)sulfinyl]-1H-benzimidazole derivative of

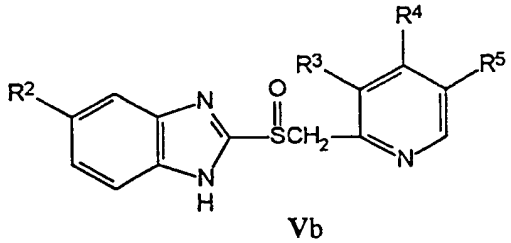
the general formula Va



Va

wherein R^2, R^3, R^4 and R^5 are as defined above, and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa, a compound of any of the formulae I, II, III and Va, if desired, being converted into a different compound of said formula before the reaction in the next step is carried out, and furthermore, if desired,

iv) reducing the obtained compound of formula Va or a salt thereof into a compound of the general formula Vb,



Vb

wherein R^2, R^3, R^4 and R^5 are as defined above,

and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa.

2. A process according to claim 1, wherein the oxidation in step i) is carried out with an oxidation agent selected from bromine, chlorine and sulfuryl chloride.

3. A process according to claim 1 or 2, wherein the oxidation in step i) is followed by addition of a trialkylamine base, preferably triethylamine.

4. A process according to one or more of the preceding claims, wherein the oxidation in step i) is

carried out at a temperature from -20°C - 70°C, preferably from 0°C - 40°C.

5. A process according to one or more of the preceding claims, wherein the oxidation in step ii) is carried out using a peroxy-type oxidation agent.

6. A process according to claim 5, wherein the peroxy-type oxidation agent is selected from peracids, preferably optionally substituted perbenzoic acids, alkylhydroperoxides, benzoylperoxides, hydrogenperoxide, tetraalkylammonium meta-periodates and perborates.

7. A process according to one or more of the preceding claims, wherein the oxidation in step ii) is carried out at a temperature from -70°C - 70°C, preferably from -20°C - 30°C.

8. A process according to one or more of the preceding claims, wherein the alcoholate used in step iii) is an alkali metal alcoholate, preferably potassium t-butoxide.

9. A process according to one or more of the preceding claims, wherein the reaction in step iii) is carried out at a temperature from -70°C - 50°C, preferably from -30°C - 30°C.

10. A process according to one or more of the preceding claims, wherein the steps i) and ii), the steps ii) and iii) or the steps i), ii) and iii) are carried out in situ.

11. A process according to one or more of the preceding claims, wherein the reduction in step iv) is carried out using a thiobisamine, dialkoxysulfane, RaNi/H_2 or Ru-catalyst/H_2 as reducing agent.

12. A process according to claim 11, wherein the reduction in step iv) is carried out using a thiobisamine as reducing agent.

13. A process according to claim 12, wherein the

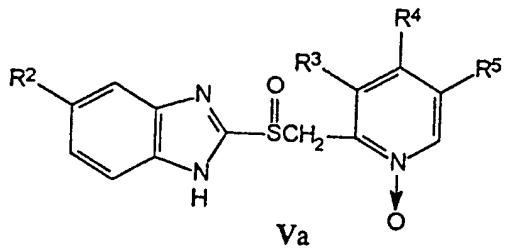
thiobisamine is used in a molar ratio to the compound of formula (Va) of 0.8 - 5.0, particularly in a molar ratio of 1.0 - 2.5 and preferably in a molar ratio of 1.0 - 1.5.

14. A process according to claim 12 or 13, wherein the reduction is carried out in an alcoholic solvent, preferably in a methanolic and/or ethanolic solvent.

15. A process according to one or more of claims 12 - 14, wherein the reduction is carried out in the presence of a mineral acid, preferably hydrochloric acid and/or sulphuric acid.

16. A process according to one or more of claims 12 - 15, wherein the reduction is carried out at a temperature in the range from -50°C - 70°C, preferably in the range from -10°C - 40°C.

17. A compound of the general formula Va



Va

wherein R^2, R^3, R^4 and R^5 are as defined above, or a salt thereof, with the provisos that R^2, R^3, R^4 and R^5 are not all hydrogen, that when R^3 is methyl and R^4 is 2,2,2-trifluoroethoxy, then R^2 and R^5 are not both hydrogen, and that when R^3 and R^5 are both CH_3, then R^2 and R^4 are not both OCH_3.

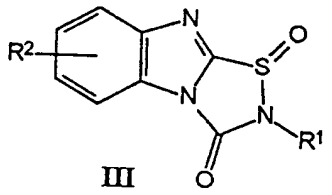
18. A compound according to claim 17, wherein

R^2 represents $OCHF_2$, R^3 and R^4 represent OCH_3 and R^5 represents H.

19. A compound according to claim 17, wherein

R^2 represents OCH_3, R^3 and R^5 represent CH_3 and R^4 represents Cl.

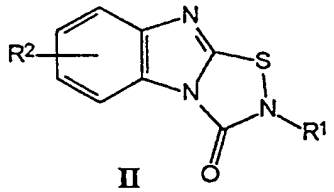
20. A compound of the general formula III,



III

wherein R^1 and R^2 are as defined above, and the R^2 group is located in the 6- or 7-position of the condensed ring.

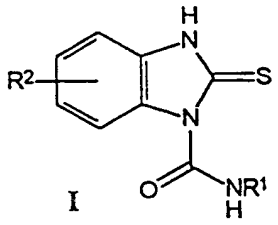
21. A compound of the general formula II,



II

wherein R^1 and R^2 are as defined in claim 20, with the proviso that R^2 is other than H, and wherein the R^2 group is located in the 6- or 7-position of the condensed ring.

22. A compound of the general formula I,

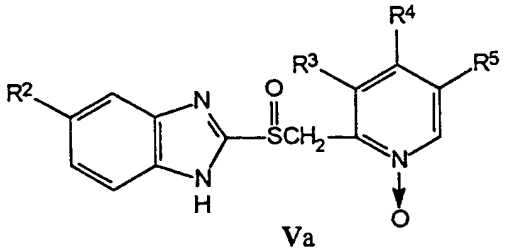


I

wherein R^1 and R^2 are as defined in claim 21.

23. A compound according to claim 20, 21 or 22, wherein R^1 is cyclohexyl.

24. The use of a compound of the general formula Va



Va

wherein

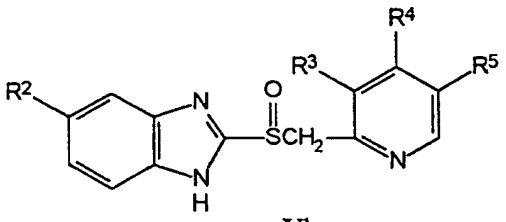
R^2 represents H, OCH_3, $OCHF_2$ or CF_3,

R^3 represents H, CH_3 or OCH_3,

R^4 represents H, OCH_3, OCH_2CF_3, halo or nitro, and

R^5 represents H, CH_3 or OCH_3,

or a salt thereof, for the preparation of a compound of the general formula Vb



Vb

wherein R^2, R^3, R^4 and R^5 are as defined above, or a salt thereof.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/DK 98/00059

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 C07D235/28 C07D513/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 484 265 A (GENESIS PARA LA INVESTIGACION ;ESTEVE QUIMICA SA (ES)) 6 May 1992 * see the whole document; in particular page 24 - page 25, examples 9 and 10 * ---	1,11-19, 24
A	D. MARTIN ET AL.: "Acylierung von Heterocyclen mit Kohlensäurederivaten-III" TETRAHEDRON, (INCL TETRAHEDRON REPORTS), vol. 39, no. 13, 1983, OXFORD GB, pages 2311-2314, XP002039564 cited in the application * see the whole document; in particular page 2311, scheme 1 * ---	1-7, 21-23
A	DD 231 787 A (AKADEMIE DER WISSENSCHAFTEN DER DDR) 8 January 1986 see the whole document ---	1,8-10, 20
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 1998	03/06/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

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INTERNATIONAL SEARCH REPORT

Inter ional Application No
PCT/DK 98/00059

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	H. KAGAMI ET AL.: "Deoxygenation of Amine N-Oxides or C-Nitroso Compounds by Dialkyl Sulfoxylates" JOURNAL OF ORGANIC CHEMISTRY, vol. 43, no. 6, 17 March 1978, EASTON US, pages 1267-1268, XP002039565 see the whole document	1,11-16

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/DK 98/00059

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0484265 A	06-05-92	NONE	
DD 231787 A		NONE	